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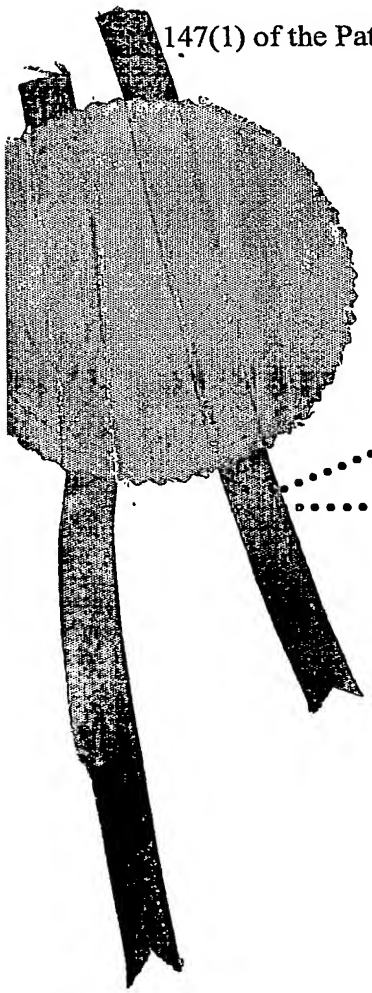
Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 29/09/2003 in respect of Patent Application No.1023/MUM/2003 of M/S. CIPLA LIMITED, 289, Bellasis Road, Mumbai Central, Mumbai – 400 008, Maharashtra, India, An Indian Company incorporated under the Companies Act 1956.

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act, 1970.



Dated this 1st day of February 2005.

(R.BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

[See section 7]

1. We,

   (a) **M/S. CIPLA LIMITED**

   (b) **289, Bellasis Road, Mumbai Central, Mumbai – 400 008, Maharashtra, India**

   (c) **Indian company incorporated under the Companies Act 1956**

2. Hereby declare –

   (a) that we are in possession of an invention titled **"PHARMACEUTICAL COMPOSITION WITH IMPROVED STABILITY"**

   (b) that the Provisional Specification relating to this invention is filed with this application.

   (c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventor(s) for the said invention are

   (a) **Lulla, Amar**

   (b) 131, Maker Tower-L
   13th Floor, Cuffe Parade
   Colaba, Mumbai 400 015
   Maharashtra, India

   (c) Indian National

   (a) **Malhotra, Geena**

   (b) 4, Anderson House,
   Opp. Mazgaon Post Office,
   Mazgaon, Mumbai 400 010
   Maharashtra, India

   (c) Indian National

72-MUM-WTO
4919, 1023

72/mum/WTO/2003

1023/mum/2003

Received Rs. 3000/- in Cash
Cheque/M.O./P.O. dt. 29/9/2003
Vide Entry No. 4919 in the Register of Valuables, Bombay.

4. That we are the assignee(s) of the true and first inventors.

5. That our address for service in India is as follows:

GOPAKUMAR NAIR ASSOCIATES, NAIR BAUG, AKURLI ROAD, KANDIVLI (EAST), MUMBAI – 400 101.

6. Following declaration was given by the inventor(s) :

We the true and first inventors for this invention in the convention country declare that the applicant(s) herein are our assignee

(Lulla, Amar)

(Malhotra, Geena)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Following are the attachment with the application:
   (a) Provisional specification (2 copies)
   (b) Statement and Undertaking on Form 3
   (c) Copy of Form 26 (Original Power of attorney in our favour has been submitted with Application No. 168/MUM/2003)
   (d) Fee Rs.3000/- in cheque bearing No. 583897 dated 29th Sept 2003 on Global Trust Bank Limited, Mumbai.

We request that a patent may be granted to us for the said invention.

Dated this the 29th day of Sept 2003

DR. GOPAKUMAR G. NAIR
Agent for the Applicant
GOPAKUMAR NAIR ASSOCIATES
Nair Baug, Akurli Road,
Kandivli(East) Mumbai – 400 101

To
The Controller of Patents
The Patent Office,
At Mumbai.

FORM 2

THE PATENTS ACT, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
[See section 10]

"PHARMACEUTICAL COMPOSITION WITH IMPROVED STABILITY"

(a) **CIPLA LTD.**

(b) **289, Bellasis Road, Mumbai Central, Mumbai – 400 008, Maharashtra, India**

(c) **Indian Company incorporated under the Companies Act 1956**

The following specification describes the nature of the invention and the manner in which it is to be performed:

PHARMACEUTICAL COMPOSITION WITH IMPROVED STABILITY.

Technical Field of the invention

The present invention relates to an improved solid oral formulation comprising of bisphosphonic acid derivatives, its process of manufacture and use thereof.

Background and Prior Art

Bisphosphonic acid derivatives are very well known to be used for treatment of skeletal disorders. These bisphosphonic acid include but are not limited to clodronic acid, pamidronic acid, alendronic acid, risedronic acid, etidronic acid, such other compounds of this class, their salts and solvates thereof. These compounds are active in calcium and phosphate metabolism mediated disorders. Alendronate sodium i.e (4-amino-1-hydroxybutylidene) bisphosphonic acid is taught by the patent DE 3,016,289. Patent number US 6,468,559 claims an enterically coated capsule housing a substantially non-aqeuous liquid or semisolid composition comprised of: (a) a therapeutically effective amount of an active agent selected from bisphosphonic acids and pharmacologically acceptable salts, hydrates and other derivatives thereof and (b) a pharmacologically acceptable, substantially non-aqeuous liquid or semisolid carrier in which the active ingredient is dissolved or suspended.

Patent number US 6,554,967 describes liquid formulation of alendronate monosodium trihydrate comprising of sodium propyl paraben, sodium butyl paraben, sodium citrate dihydrate, citric acid anhydrous, sodium hydroxide to adjust pH and water as a vehicle.

Alendronic acid as monosodium salt trihydrate is an active ingredient of the pharmaceutical oral dosage formulation known as Fosamax®, indicated for the treatment and prevention of osteoporosis. Beside the active substance this formulation comprises of

microcrystalline cellulose, anhydrous lactose, croscarmellose sodium and magnesium stearate as the excipients.

Lactose, which is used in Fosamax®, in its anhydrous form, is generally used as filler for solid dosage forms due to its excellent compressibility, high purity and stability. However patent number WO 0185176 cites that this substance may generate formulation incompatibilities with the primary or secondary amine group containing compounds. The incompatibilities are caused by the reaction between the reducing aldehyde moiety of lactose and the amine group present in the active ingredient, known as the Maillard reaction. The resulting degradation products are inactive. The formation of the said products is evidenced by a brown coloring of the final drug dosage forms. The presence of water enhances the degradation. [(Reference: Handbook of Pharmaceutical Excipients, 2nd edition, 1994, pg. 257 (ISBN 091730 60 8)].

The bisphosphonic acid derivatives such as alendronic acid derivatives, etidronic acid derivatives, clodronic acid derivatives, pamidronic acid derivatives, risedronic acid derivatives contain an amine group in their molecule. The problem of browning of lactose containing dosage form with alendronic acid and other bisphosphonic acid derivatives with a primary or a secondary amine group was disclosed in the International Patent Publication No. WO 94/12200. This patent proposes the method of avoiding the interaction of bisphosphonic acid derivatives comprising an amine group in the molecule with lactose by providing the dry composition of the active ingredient and lactose and the process of preparation thereof comprising the direct blending of the said dry mix without granulation or addition of water before compression.

Prior art US 5,358941, US 6,090,410 and US 5,681,590 granted to Merck & Co. claim a dry mix for bisphosphonic acids along with lactose in which lactose used is essentially anhydrous. The method as described for preparation of the formulation of these inventions is direct compression of said dry mix.

Patent number US 5,849,726 and US 6,008,207 describe a formulation of anhydrous bisphosphonic acid derivative, viz, anhydrous alendronate monosodium along with anhydrous lactose and microcrystalline cellulose. The method of preparation as described therein is direct compression of a dry mix formulation comprising of the active ingredient lactose and other ingredients such as microcrystalline cellulose, magnesium stearate and crosscarmellose sodium.

Although patent WO 01/85716 appreciated these prior arts for their ingenuity in attempting stabilize the formulations, it still stated that the direct compression method of preparing these formulations, did not however solve the instability problem of these pharmaceutical preparations during long storage, especially in warm and damp conditions. Therefore this patent describes a wet granulation method for preparation of a bisphosphonic acid derivative along with a carbohydrate alcohol such as D-mannitol. But the manner of preparing the dosage form does not bring the bisphosphonic acid derivative and mannitol directly in contact with water. The patent describes preparing a core of mannitol and cross-linked polyvinylpyrolidone and polyvinylpyrolidone by wet granulation and drying this core to obtain granules. This core is then combined with the active ingredient with the lubricant and other excipients. This blend is then compressed to form tablets.

Therefore, it is clearly evidenced that the inventor although claiming a wet granulation process of preparation of the said dosage form still anticipates degradation when the bisphosphonic acid derivative along with mannitol are intimately mixed with water or any such aqueous solvents.

Surprisingly, it has been found that a stable formulation comprising of bisphosphonic acid derivative can be prepared by intimately mixing it with a carbohydrate alcohol and water and such aqueous solvents. The formulation so prepared by a simple technique is highly stable and does not result in degradation of the bisphosphonic acid derivative.

The present invention is therefore aimed at providing a stable formulation of a bisphosphonic acid derivative along with one or more carbohydrate alcohol using water or aqueous based solvents for manufacture.

The bisphosphonic acid derivatives may be selected from alendronic acid, etidronic acid, clodronic acid, risedronic acid, pamidronic acid and such other compounds of this class which are susceptible to degradation with lactose resulting in browning of the dosage form, their salts, derivatives, enantiomers, prodrugs, racemic mixtures thereof.

The carbohydrate alcohols may be selected from mannitol, sorbitol, erythritol, xylitol, and such other compounds of this class, which do not contain a reducing aldehyde moiety in their chemical structure, their isomers and racemic mixtures thereof.

The formulation as provided by the present invention can be used in the treatment of various skeletal diseases such as systemic bone diseases like osteoporosis, osteoarthritis, Paget's disease, osteomalacia, multiple myleloma, and other forms of cancer, steroid, therapy and age-related loss of bone mass, local disorders such as bone fractures and such other related disorders.

It is another object of the present invention to provide a simple method of manufacturing a stable formulation, which does not result in degradation of the bisphosphonic acid derivatives.

The method as provided by the invention involves mixing intimately the bisphosphonic acid derivative along with at least one carbohydrate alcohol and granulating with a suitable binding agent along with water or such aqueous solvents for preparing the granules.

It is also provided by the present invention a formulation comprising of the active ingredients in therapeutic range so as to produce adequate therapeutic efficacy and subsequent relief in treatment of skeletal diseases such as systemic bone diseases like

osteoporosis, osteoarthritis, Paget's disease, osteomalacia, multiple myleloma, and other forms of cancer, steroid, therapy and age-related loss of bone mass, local disorders such as bone fractures and such other related disorders.

Summary of the invention

The present invention comprises of an improved stable formulation comprising of bisphosphonic acid derivatives as the active ingredient, at least one carbohydrate alcohol along with water or such aqueous solvents, its method of preparation and use thereof.

Detailed Description

The said formulation as mentioned may be prepared as tablets, capsules, tablets in capsules, pellets and such other solid oral dosage form.

The active ingredient may be selected from 4-amino-1- hydroxybutylidene) bisphosphonic acid derivative, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] derivative, (1-hydroxyethylidene) diphosphonic acid derivative, 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid derivatives, their salts, prodrugs, enantiomers and racemic mixtures thereof. The salts as mentioned may be selected from group I metals.

The active ingredients may be used in the range of 0.5% to 40% with respect to the formulation. Along with the active ingredient, additional intragranular excipients such as diluent like a carbohydrate alcohol and celluloses, disintegrants, superdisintegrants may be employed. The carbohydrate alcohol is selected from mannitol, lactitol, sorbitol, erythritol, xylitol, maltitol, and such other compounds of this class, their enantiomers, diastereomers, and racemic mixtures thereof. The carbohydrate alcohol and the cellulose are used in the ratio of 25:75 to 75:25. The intragranular ingredients maybe converted to granules by using suitable binders selected from natural and synthetic gums, celluloses such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethyl

cellulose sodium, polyvinylpyrolidones, starches, gelatins and povidones and such other pharmaceutically acceptable substances with cohesive properties. The binder solution can be prepared using water and such other aqueous based solvents.

The granules may be further lubricated by employing lubricants selected from talc, magnesium stearate, stearic acid, hydrogenated vegetable oils, glyceryl behenate, polyethylene glycols and their derivatives sodium lauryl sulphate, sodium stearyl fumarate, sodium starch glycollate and the like.

The dosage forms as prepared contain the active ingredient in therapeutic range. The said formulation can be used to treat humans, particularly females who are post-menopausal, with an osteogenically effective amount of the bisphosphonic acid derivatives to inhibit bone resorption in need of such treatment. The term "bone resorption" as used herein, refers to treatment and prevention of bone loss, especially inhibiting the removal of existing bone either from the mineral phase and / or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity. Thus, the term "inhibitor of bone resorption" refers to agents that prevent bone loss by the direct or indirect alteration of osteoclast formation or activity and which may increase bone mass in the patient treatment populations. The term "osteogenically effective" as used herein, means that the amount, which affects the turnover of mature bone. As used herein, an osteogenically effective dose is also "pharmaceutically effective".

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be falling within the scope of the invention.

The following examples are for the purpose of illustration of the invention only and are not intended in any way to limit the scope of the invention.

Example 1

SR. NO.	INGREDIENTS	QTY/TAB (mg)	QTY/TAB (mg)
	INTRAGRANULAR INGREDIENTS		
1.	Alendronate Sodium Trihydrate equivalent to alendronic acid	35	70
2.	Microcrystalline cellulose	57.5	115.0
3.	Mannitol	58.32	116.63
4.	Sodium Starch Glycollate	7.5	15.0
	BINDER SOLUTION		
5.	Starch	1.5	3.0
6.	Purified Water	q.s.	q.s.
	EXTRAGRANULAR INGREDIENTS		
7.	Magnesium Stearate	2.00	4.00
8.	Sodium Starch Glycollate	2.5	5.00
	TOTAL	**175.00**	**350.00**

PROCESS:

Pre-sifted Alendronate sodium trihydrate, sodium starch glycollate, mannitol, microcrystalline cellulose were dry-mixed in the Fluidised Bed Processor for 5 mins. Binder solution was prepared using starch and purified water. This binder solution was then sprayed over the drymix at a specified rate and temperature to obtain granules. The granules were then spray dried and sifted. The granules were then blended in the IPC blender along with sodium starch glycollate and pre-sifted magnesium stearate. The granules were then compressed to form tablets.

Example 2:

SR. NO.	INGREDIENTS	QTY/TAB (mg)
	INTRAGRANULAR INGREDIENTS	
1.	Etidronate disodium equivalent to etidronic acid	200
2.	Microcrystalline cellulose	158.20
3.	Mannitol	156.64
4.	Sodium Starch Glycollate	20.14
	BINDER SOLUTION	
5.	Starch	4.0
6.	Purified Water	q.s.
	EXTRAGRANULAR INGREDIENTS	
7.	Magnesium Stearate	5.52
8.	Sodium Starch Glycollate	5.5
	TOTAL	**550.00**

Process:

Pre-sifted Etidronate disodium, sodium starch glycollate, mannitol, microcrystalline cellulose were dry-mixed in the Fluidized Bed Equipment for 5 mins. Binder solution was prepared using starch and purified water. This binder solution was then sprayed over the drymix at a specified rate and temperature to obtain granules. The granules were then spray dried and sifted followed by mixing them in the IPC blender along with sodium starch glycollate and pre-sifted magnesium stearate. The granules were then filled in capsules.

Example 3:

SR. NO.	INGREDIENTS	QTY/TAB (mg)
	INTRAGRANULAR INGREDIENTS	
1.	Risedronate sodium monohydrate equivalent to Risedronic acid.	30
2.	Microcrystalline cellulose	45.3
3.	Mannitol	55.6
4.	Sodium Starch Glycollate	4.9
	BINDER SOLUTION	
5.	Starch	1
6.	Purified Water	q.s.
	EXTRAGRANULAR INGREDIENTS	
7.	Magnesium Stearate	1.3
8.	Sodium Starch Glycollate	1.6
	TOTAL	140.00

Process:

Pre-sifted Risedronate sodium monohydrate, sodium starch glycollate, mannitol, microcrystalline cellulose were dry-mixed in the Fluidized Bed Equipment for 5 mins. Binder solution was prepared using starch and purified water. This binder solution was then sprayed over the dry mix at a specified rate and temperature to obtain granules. The granules were then spray dried and sifted followed by mixing them in the IPC blender along with sodium starch glycollate and pre-sifted magnesium stearate. The granules were then filled in capsules.

While the present invention is described above in connection with preferred or illustrative embodiments, these embodiments are not intended to be exhaustive or limiting of the invention. Rather, the invention is intended to cover all alternatives, modifications and equivalents included within its spirit and scope.

Dated this the 29th day of Sept 2003

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To

The Controller of Patents
The Patent Office,
At Mumbai.

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